REMARKS

Claims 1-74 are pending in the application with claims 1, 2, 4-33 and 35-43 currently under examination. Claims 3 has been previously cancelled without prejudice. Claims 34 and 44-74 stand withdrawn from consideration as being directed to a non-elected invention. Claims 1, 16 and 32 have been amended. Support for the amendments can be found throughout the application as filed including, for example, at page 31, lines 4-6; page 31, lines 6-10; page 18, lines 22-26; page 3, lines 24-27; page 25, lines 14-15, and page 20, lines 3-8. In claim 1, among other things, the step (a) of 'producing a comparison' has been amended and separated into a 'producing' step (a) and a 'comparing' step (b) in that claim. New claims 75, 76 and 77 have also been added. Support for these new claims can be found in amended claims 1, 16 and 32 and previously presented claim 13, 28 and 40 respectively. Without prejudice against seeking broader claims in a continuation application, Applicants seek to enter the above amendments to place the application in better form for allowance. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicant has reviewed the rejections set forth in the pending Office Action, and respectfully traverse all grounds for the reasons that follow.

Rejection Under 35 U.S.C. § 102 Over Rine et al.

Claims 1, 2, 4-33 and 35-43 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Rine et al. The Office maintains that Rine et al. describe analyzing stimulus-response patterns of a living thing using artificial intelligence systems and cites various passages which are alleged to anticipate all elements of the claimed invention. The Office concludes that the distinction argued of record in previous Responses is addressed in various cited passages of the rejection. Applicant respectfully traverse and will address the relevant passages in turn below.

In particular, the Office fails to give patentable weight to Applicants' showing that Rine et al. compare values obtained from the same type of responders. Although several types of responders such as genes, gene regulatory elements, gene transcripts, or gene translates, or a predetermined functional class or subset of the organism's entire repertoire as well as sufficient ensemble of responders to deduce the action of a stimulus are disclosed in column 2, lines 30-44,

Rine et al. fail to teach or suggest either the integration or the association of values from any two or more of these responders with each other. The Office has found the previous responses of record unpersuasive allegedly because "the claims do not state the results have to relate back to each other." The 05/09/2007 Office Action, at page 8.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131 (quoting *Verdegaal Bros. v. Union Oil Co.* of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)) (emphasis added). A rejection under § 102 is proper only when the claimed subject matter is identically described or disclosed in the prior art. *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972); M.P.E.P. § 706.02.

Applicants submit that in view of amended claims 1, 16, and 32, the Office has failed to establish that each and every element of the claims is either expressly or inherently described in Rine et al. Specifically, claims 1, 16, and 32 as amended recite that each data integration map is generated by integrating value sets containing two or more different types of data elements and that correlative changes in at least two value sets are identified relative to one or more of the value sets (emphasis added). However, as previously asserted, Rine et al. produce a database of the same type of data and compare that same type of data elements obtained under different conditions.

For example, in Figure 6, Rine et al. use a gene reporter matrix —a physical matrix with a single type of responder (data element) —to compare the effects of an unknown stimuli with that of the mutation, which represent two different conditions (cols. 11-12). Similarly, in Figure 7, Rine et al. use a gene reporter matrix —again a physical matrix with a single type of responder or data element —to compare the genetic response profile of a new chemical stimulus with the genetic response profile of known chemical stimuli or a target mutant gene (col. 12, lines 5-65). In both of the above instances as well as elsewhere in the disclosure as cited on page 6 of the Office Action, Rine et al. compare the values obtained from the same type of responder (e.g., gene transcripts) under different conditions or in response to different stimuli. Therefore, Rine et al. fail to teach the elements of "each data integration maps is generated by integrating value set

containing two or more different types of data elements" and "identifying correlative changes in at least two value sets relative to one or more of the value set."

The Office on page 3 of the Office Action contends that Rine et al. in col. 2, lines 4-28, disclose "detecting a physical signal (value) at each unit of the physical matrix (data integration map . . .) . . . and storing the output . . . and comparing the output signal matrix to an output signal matrix database (other matrices) which represents producing a comparison of two or more data integration maps obtained under different conditions." However, as indicated previously, the cited passage is silent as to any comparison between output signal matrices generated from different types of responders.

Rine et al. fail to describe an integration map having such two or more value sets containing different types of data elements and, similarly, fail to describe that the value sets are integrated and their correlative changes are identified relative to one or more of the value sets. Absent any description in Rine et al. of generating and combining different types of data into a value set as Applicants' claim, Rine et al. cannot anticipate the invention as claimed.

The Office further contends on page 7 of the Office Action that Rine et al. "disclose using an array containing a different responder of a living thing in each unit which may comprise an organism's entire repertoire of responders." Applicants respectfully points out that even if Rine et al. disclose the use of a living organism in each unit, which may comprise many different responders, Rine et al. still fail to disclose whether values from different types of responders are detected and compared or whether the correlative changes in at least two value sets are identified relative to one or more of the value sets. Accordingly, upon failing to teach each and every element of the claimed invention, Rine et al. cannot anticipate the invention as claimed. Withdrawal of this ground of rejection is respectfully requested.

Rejection Under 35 U.S.C. § 102 Over Thalhammer-Reyero

Claims 1-2, 4-33 and 33-43 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Thalhammer-Reyero (U.S. Publication No. 2005/0273305). The Office alleges that Thalhammer-Reyero describes methods for modeling and simulation of various biochemical networks and pathways and cites various passages and claims which are alleged to anticipate all

elements of the claimed invention. Applicants respectfully traverse and will address the relevant passages and claims in turn below.

The Office, on pages 10-11 of the Office Action, makes references to claims 142, 259-262 and 412-414 in Thalhammer-Reyero in support of its allegations. Applicants respectfully point out to the claims cited for support were expressly copied in a parent application to the cited reference on June 2, 2003, and on February 24, 2004, from U.S. Publication Nos. 20020068269 and 20030130798 (subject application), and were added to the cited reference in a preliminary amendment filed October 23, 2006. A copy of the preliminary amendment is attached for the record (Exhibit 1). Applicants further draw the Examiner's attention to the Remarks section of the Preliminary Amendment where no apparent support is provided for the copied claims. Applicants respectfully submit that none exists. Because the cited claims in Thalhammer-Reyero are not supported in the application as filed Thalhammer-Reyero is not prior art under § 102(e) as to this subject matter.

The Office contends on page 9 of the Office Action that the abstract on Thalhammer-Reyero states the preamble of instant claim 1. Applicants again respectfully point out that this abstract was entered by the above Preliminary Amendment. As with the above cited claims, no support for this amendment also was provided. Applicants again respectfully submit that none exists. Accordingly, Thalhammer-Reyero is not prior art under § 102(e) as to this subject matter.

The Office further alleges on page 10 that the Thalhammer-Reyero disclosure provides output (0036, 0097, 0140); that it discloses data elements corresponding to physical interactions (0017), as stated in instant claims 5 and 20; that it discloses inverse changes (0434, 0514), as stated in instant claims 12, 27 and 39; that it shows five components in Figure 2, as stated in instant claims 14, 29 and 31; that it discloses allowing repeated use of entities as building blocks in a variety of situations (0094, 0141 and 0576), as stated in instant claims 30 and 42. In all of the above instances, the Office makes references to the dependent claims.

The further citation of support in Thalhammer-Reyero cannot anticipate these dependent claims absent some teaching in the application as to each and every element of their base claim. As set forth above, Thalhammer-Reyero is not prior art as to the claimed invention. Therefore, withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

In light of the Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP

/David A. Gay/

David A. Gay
Registration No. 39,200

4370 La Jolla Village Drive, Suite 700
San Diego, CA 92122
Phone: 858.535.9001 DAG:llf
Facsimile: 858.597.1585
Date: November 9, 2007

Please recognize our Customer No. 41552 as our correspondence address.

SDO 75143-1.066661.0036

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	Thalhammer-Reyero, Cristina	Art Unit:	2121
Application No.:	11/004,500	Examiner:	Unknown
Filed:	December 5, 2004	Date:	July 10, 2005
For:	Network Models of Biochemical Pathways	Customer No.	40182

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PRELIMINARY AMENDMENT UNDER 37 CFR §1.115

Sir:

Before initial examination of the above captioned patent application, please enter **Amendments to the Specification** as indicated on page 2 of this paper, and **Amendments to the Claims** as indicated in the listing of claims beginning on page 3 of this paper.

Remarks begin on page 12 of this paper.

EXHIBIT 1

U.S. 11/004,500
Replacement Abstract filed 07/14/2005

ABSTRACT

This invention describes computer based systems and methods for modeling and simulation of biochemical networks of pathways, including metabolic, signal transduction and regulatory pathways within a cell or across cells. The invention comprises systems and methods for building the models and for using the models for analysis and information retrieval, for determining the effect that modulating one or more reactions in a biochemical pathway has on an operation of the biochemical pathway, and for simulating or predicting an altered physiological state of cells.

Amendments to the Specification

Replace the paragraph under the title COMPACT DISC APPENDIX on the first page of the specification with the following paragraph:

The Tables 1-233 referenced in the specification are pseudo-code listings provided in the Appendix contained in the CD-R Disc, which comprises one file of 453 KB, created on 09/14/2004 and labeled Divisional_of_08860975_ProgramCode.txt. The file is a text file compatible with the Windows operating system.

Listing of Claims:

This listing of claims will replace all prior versions of claims in the application:

What is claimed is:

142 (currently amended) A method of determining in a computer system an effect that modulating one or more reactions in a biochemical pathway has on an operation of the biochemical pathway, comprising a) generating ~~and displaying~~ a first representation of a ~~first~~ biochemical pathway by dynamically determining substances and processes that form the ~~first~~ biochemical pathway, and an order in which the substances appear and the processes occur in the ~~first~~ biochemical pathway; b) generating ~~and displaying~~ a second representation of ~~a second~~ the biochemical pathway, wherein a definition of at least one substance or process of the first biochemical pathway is changed so as to modulate at least one reaction of the first biochemical pathway; and c) comparing the first and second representations of the ~~first and second~~ biochemical pathway[[[s]]] and determining an effect of modulating the at least one reaction of the ~~first~~ biochemical pathway.

143 canceled

149-154 canceled

161 (currently amended) A computer readable medium or media, comprising: a) a ~~data structure~~ model relating a plurality of reactants to a plurality of reactions ~~of~~ representing a biochemical reaction network, wherein ~~each~~ a plurality of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of

said reactions is a regulated reaction; ~~and~~ b) a constraint set for said plurality of reactions, wherein said constraint set comprises a variable constraint for said regulated reaction, wherein said constraint set when applied to said plurality of reactions by program instructions in a computer system results in a model of said biochemical reaction network.

162 (currently amended) The computer readable medium or media of claim 161, further comprising a regulatory data structure representing an event that regulates the biochemical reaction network, wherein said variable constraint is dependent upon an outcome of ~~a regulatory event represented by~~ said regulatory data structure.

163 (currently amended) The computer readable medium or media of claim 162, wherein said biochemical reaction network represents reactions that occur in a first cell in a population of cells and said regulatory data structure represents one or more events that occur in a second cell in said population.

164 (currently amended) The computer readable medium or media of claim 162, further comprising a user interface capable of sending at least one program instruction ~~command~~ for modifying said data structure, said constraint set or said program instructions ~~commands~~ for applying said constraint set to said data representation, or a combination thereof.

165 canceled

166 (original The computer readable medium or media of claim 161, wherein a first substrate or product in said plurality of reactions is assigned to a first compartment and a second substrate or product in said plurality of reactions is assigned to a second compartment.

167-191 canceled

211-215 canceled

218-219 canceled

221 (currently amended) A method of predicting an altered physiological state of a cell comprising the steps of: a) specifying a biochemical network of a cell; b) simulating said network by specifying the components of said network, and representing interrelationships between said components in one or more mathematical equations and setting the quantitative parameters of said components; c) ~~optimizing said first simulated biochemical network by determining and~~ constraining the values of the parameters of said components to represent a first state of the cell; d) perturbing the ~~optimized~~ simulated network by adding or deleting one or more components thereof, changing the concentration of one or more components thereof or modifying one or more mathematical equations representing interrelationships between one or more of said components; e) solving the equations representing the perturbed network to simulate a second state of the cell; and f) comparing said first and second simulated states of the network to identify the effect of said perturbation on the state of the cell ~~network~~.

222 (currently amended) The~~A~~ method of ~~as recited in~~ claim 221 including the steps of storing said mathematical equations in computer memory, storing algorithms in computer memory for solving said mathematical equations, said solving step or steps each comprising retrieving said algorithms and applying them to solve said equations ~~including the step of storing optimization algorithms in computer memory, storing in computer memory values corresponding to said quantitative parameters, and applying said algorithms to said parameters to optimize said simulated biochemical network~~.

225-227 canceled

234-235 canceled

240-246 canceled

247-248 canceled

249-250 canceled

251-252 canceled

259 (currently amended) A method of predicting a behavior of a biochemical system, comprising: a) obtaining a first data integration map of a biochemical system, said data integration map comprising value sets of two or more data elements for at least ~~two~~ one network[[s]]; b) producing a second data integration map of said biochemical system under a perturbed condition, said second data integration map comprising ~~said~~ perturbed value sets of two or more data elements for said at least ~~two~~ one network[[s]], and c) identifying correlative changes in at least two value sets in said second data integration map with said perturbed condition, wherein said correlative changes predict a behavior of said biochemical system.

260 (original) The method of claim 259, wherein said biochemical system is selected from the group consisting of a cell, tissue and organism, or a constituent system thereof.

261 (original) The method of claim 259, wherein said second data integration network further comprises two or more perturbed conditions.

262 (original) The method of claim 259, wherein said behavior is selected from the group consisting of cellular phenotype, biochemical activity, expression level and accumulation level.

263-264 canceled

270 (currently amended) A system for constructing a scalable output network model of a ~~complex~~ biological system or subsystem, comprising: a) an input data set of network components comprising a ~~network~~ set of components representing genes and/or gene products ~~components~~; b) executable instructions forming a data structure associating said network components with network process/reaction components, said data structure establishing a data set specifying a network model of connectivity and direction of flow of said network ~~process/reaction components; and c) executable instructions mathematically describing from said data set said network model of connectivity and flow~~, wherein said ~~mathematical~~ topological description defines a scalable output network model of the complex biological system or subsystem.

271 (original) The system of claim 270 wherein said output network model is a scalable phenotypic output network model of a living organism or component, further comprising executable instructions modifying said data set to fit a set of desired constraints on said specified network model, wherein said set of desired constraints define a phenotypic output of said network model of a living organism or component.

394 (new) A computer-implemented method of predicting biological pathways comprising: (a) modeling components of signal cascades of pathways that occur when stimuli are introduced; (b) dynamically generating results using a simulation module, the simulation module comprising an inference engine linked to at least one dynamic database, the at least one dynamic database containing definitions relating to cellular concepts, components and reactions.

395 (new) The computer-implemented method of claim 394 wherein said definitions of concepts, components and reactions are organized in a hierachical ontology

396 (new) The computer-implemented method of claim 394 wherein instances of said concepts, components and reactions are organized in a modular hierarchy.

397 (new) The computer-implemented method of claim 394c wherein said modules in the hierarchy represent functional, locational or temporal compartments, or any combination thereof.

398 (new) The method of claim 142 wherein said generating a first representation of a biochemical pathway further comprises dynamically selecting the substances and/or processes of said biochemical pathway from a database of substances and/or processes.

399 (new) The method of claim 142 wherein said representations of the biochemical pathway further comprise quantitative variables, further comprising applying algorithms for solving mathematical equations over said variables to quantitatively determining an effect of modulating the at least one reaction of the biochemical pathway

400 (new) The method of claim 142 wherein said biochemical pathway spans two more cellular compartments, cells, organs, physiological systems or organisms.

401 . (new) The method of claim 142 applied to identifying a potential pharmacological target in the biochemical pathway that affects a physiological or pathological condition of an organism, further comprising determining a substance participating in a reaction or a process which, when modulated, alters the biochemical pathway in a desired manner, wherein the substance or process is a potential target for a drug.

402 (new) The method of claim 142 applied to identifying a potential pharmacological agent that act upon the biochemical pathway to affects a physiological or pathological condition of an organism, further comprising determining an agent which modulate one or more process or

substance participating in a reaction to alter the biochemical pathway in a desired manner, wherein the agent is a potential drug.

403 (new) The computer readable medium or media of claim 161, further comprising program instructions to apply said constraint set to said plurality of reactions in a computer system to generate a model of said biochemical reaction network.

404 (new) The computer readable medium or media of claim 161, wherein said biochemical reaction network further comprises regulatory reactions.

405 (new) The computer readable medium or media of claim 161, wherein said biochemical reaction network further comprises signal transduction pathways.

406 (new) The computer readable medium or media of claim 161, wherein said data structure further comprises at least one equation selected from the group of linear algebraic equation, differential equation and stochastic equation.

407 (new) The computer readable medium or media of claim 161, wherein a first substrate or product in said plurality of reactions is assigned to a first compartment and a second substrate or product in said plurality of reactions is assigned to a second compartment.

408 (new) The computer readable medium or media of claim 162, wherein the regulatory data structure represents a time dependent event.

409 (new) The computer readable medium or media of claim 162, wherein the regulatory data structure represents an event dependent on one or more of said reactions.

410 (new) The computer readable medium or media of claim 162, wherein the regulatory data structure represents an event dependent on the state of one or more of said reactants.

411 (new) The method of claim 221 wherein the components of said network are dynamically retrieved from a database of components.

412 (new) The method of claim 259, wherein said at least one network further comprises two or more networks.

413 (new) The method of claim 259, wherein said correlative changes in at least two value sets in said second data integration map further comprise correlative changes in three or more value sets.

414 (new) The method of claim 259, wherein said correlative changes in at least two value sets within said second data integration map further comprise value sets selected from the group consisting of protein expression, polypeptide-polypeptide interaction, nucleic acid-polypeptide interaction, metabolite abundance, and growth rate.

415 (new) The system of claim 270 wherein said output network model comprises at least one network component and network process/reaction component representing a component and a process or reaction not intrinsic to said biological system or subsystem.

416 (new) The system of claim 270 wherein said data structure comprises reactants and products.

417 (new) The system of claim 270 further comprising executable instructions mathematically describing from said data set said network model of connectivity and flow,

wherein said mathematical description defines a scalable output network model of the biological system or subsystem.

418 (new) The system of claim 417 wherein said data structure comprises reactants, products and stoichiometric coefficients.

419 (new) The system of claim 417 wherein said mathematical description comprises stochastic or differential equations, or a combination thereof.

REMARKS

This Preliminary Amendment is being filed prior to examination of the claims in the captioned application. Claims 142-143, 149-154, 161-191, 211-215, 218-219, 221-222, 225-227, 234-235, 240-252, 259-264 and 270-271 are pending in the instant application as originally filed, and were included in the parent application, U.S.S.N. 08/860,975, from which this divisional application claims benefit of priority. The following claims were copied on 06/02/2003 from US publications: claims 141-143 from 20020068269 published 06/06/2002; claims 149-154 from 20030009099 published 01/09/2003; claims 161-174 from 20030059792 published 03/27/2003. The following claims were copied on 02/24/2004 from US publications: claims 211-224 from 20030215786 published 11/20/2003; claims 225-238 from 20040029149 published 0212/2004; and claims 253-264 from 20030130798 published 07/10/2003.

By this amendment, claims 143, 149-154, 165, 167-191, 211-215, 218-219, 225-227, 234-235, 240-252 and 263-264, have been canceled as drawn to non-elected matter, and claims 142, 161-164, 221-222, 259 and 270 have been amended, without prejudice or disclaimer of any previously claimed subject matter. New claim 394 corresponds to claim 141 of the parent application. Additional new claims 395-419 are added to distinctly claim particular embodiments of the elected invention. Thus, upon entry of the instant amendment, claims 142, 161-164, 166, 221-222, 259-262, 270-271 and 394-419 will be pending. Claims 142, 161, 221, 259, 270 and 394 are independent.

The claim amendments and the new claims are fully supported in the instant application as originally filed, throughout the specification as well as in the pseudo-code listing in the CD-R.

Therefore, no new matter has been added. Entry of the above-made amendments into the file history of the instant application is respectfully requested.

The amendments or any further limitations that might have been introduced in the claims are not for patentability reasons, but rather for clarification and without prejudice. With respect to all amendments and canceled claims, Applicant has not dedicated or abandoned any unclaimed subject matter. Applicant expressly reserves the right to pursue the presently excluded subject matter or claim embodiments in one or more continuation or divisional patent applications. Applicant believes that independent claims 142, 161, 221, 259, 270 and 394 are now ready for allowance. All other claims depend on those claims and are therefore allowable for at least the same reasons. Furthermore, each of said dependent claims add additional limitations over the independent claims, and Applicant submits that each of these additional limitations over the independent claims makes each of those claims further distinguishable over the prior art.

Early examination of the present application, as amended, is courteously solicited. The Examiner is respectfully requested to contact the undersigned by telephone at the below listed number, in order to expedite resolution of any issues and to expedite passage of the present application to issue, if any comments, questions or suggestions arise in connection with the present application.

Respectfully submitted,

Cristina Thalhammer-Reyero,
Inventor/Applicant
202-257-9351